REMARKS

Favorable reconsideration, reexamination, and allowance of the present patent application are respectfully requested in view of the foregoing amendments and the following remarks. The foregoing amendments have full support in the specification and original claims, at least, at paragraph [0008]. No new matter is entered.

Amendments

Claims 1-5 are currently amended. Claims 7-19 are withdrawn. Claims 1-6 are under examination.

Objection to the Claims

At page 2 of the Office Action, Claims 2-5 were objected to because they allegedly contain informalities. Applicant respectfully requests reconsideration of this objection.

Claims 1-5 have been amended to address these objections.

For at least the foregoing reasons, Applicant respectfully submits that Claims 2-5 are not objectionable, and therefore respectfully requests withdrawal of the objection thereto.

Rejection under 35 U.S.C. § 112, first paragraph

In the Office Action, beginning at page 3, Claims 1-6 were rejected under 35 U.S.C. § 112, first paragraph, as reciting subject matters that allegedly fail to comply with the scope of enablement requirement. Applicant respectfully requests reconsideration of this rejection.

Although Applicants do not necessarily agree with the basis for this rejection, the claims have been amended to a scope deemed acceptable by the Examiner. Specifically, the claimed method recites identifying compounds that promote the capability of osteoblasts to from an extracellular matrix. It is asserted that the claimed method is fully enabled by the specification, and that one of ordinary skill in the art would be enabled to practice the invention without undue experimentation.

For at least the foregoing reasons, Applicant respectfully submits that Claims 1-6

fully comply with 35 U.S.C. § 112, first paragraph, and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 112.

Rejections under 35 U.S.C. § 102

In the Office Action, beginning at page 6, Claims 1-4 were rejected under 35 U.S.C. § 102(b), as reciting subject matters that allegedly are anticipated by Amaar et al. (hereinafter "Amaar"), and claims 1-5 were rejected under 35 U.S.C. §102(b) as being anticipated by Lai et al. (hereinafter "Lai"). Applicant respectfully requests reconsideration of this rejection.

It is respectfully noted that neither Amaar nor Lai teach or suggest a screening method, but merely recognized the effect of Fhl2 overexpression. Since these references do not teach each and every aspect of the invention, either inherently or explicitly, they cannot anticipate the claims.

In addition, both Amaar and Lai fail to show expression of Fhl2 in osteoblasts *in situ*. Amaar describes detection of expression of Fhl2 by Northern Blot (page 12056, Figure 3) and Western Blot (page 12057, Figure 4) in permanent cell lines. These cell lines are either permanent cell lines which were obtained from osteosarcomas of human origin (U-2 OS, MG-63, Saos) or primary cell lines which stem from the calvaria and the ribs and have been passaged three to four times (page 12054, right-hand column, third paragraph). Contrary thereto, the inventors show that expression of Fhl2 *in situ* can be detected in osteoblasts in the bone of mice.

Although the claims are directed to the identification of a compound which can form an extracellular matrix in osteoblasts *in vivo*, it was clearly unknown in the prior art whether the *in vitro* effects can really be applied to an *in vivo* situation. Applicants have clearly shown that Fhl2 has an effect both *in vitro* and *in vivo*. Furthermore, the disclosures of these two citations cannot be anticipatory of the claimed invention because the detection *in vivo* verus *in vitro* is not just a mere technical difference. The inventors have shown that Fhl2 expression can be induced in all tissues examined by the inventors to date, as soon as the cells are taken into culture, irrespective of whether or not the tissue already expresses Fhl2 *in vivo*. Furthermore, Amaar only mention expression in human osteoblasts, but not *in vivo* expression of Fhl2 in osteoblasts. Thus, induction of Fhl2

expression in cell culture cells is an indirect and unspecific effect which does not allow any conclusion with regard to the role in bone formation.

Amaar present the hypothesis that IGFBP-5 may bind to Fhl2, a transcription modulator, to stimulate transcription of putative IGFBP-5 target genes that may be involved in regulation of osteoblast cell proliferation and differentiation (page 12059, right-hand column, last sentence of second paragraph). While this hypothesis is regarded as speculative by the authors themselves, it clearly refers to a role of Fhl2 on proliferation and differentiation of osteoblast precursors. It is therefore perfectly possible that there is a general effect of Fhl2 on the cell division rate and on the differentiation process as it has been described for Fhl2 in multiple cell culture systems from varying tissues. This general *in vitro* effect of Fhl2 would inevitably have some effect on osteoblast precursors in the form of an indirect and unspecific effect on the mineralization and expression of osteocalcin after these cells have differentiated into mature osteoblasts.

The increase observed in proliferation and differentiation in cell culture observed by Lai after overexpression of Fhl2 is most likey an unspecific general effect found in many different cell culture systems using cells from various origins. Accordingly, one of ordinary skill in the art would not have expected that the effects observed by Lai to be specific or applicable to bone cells. Other groups have been unable to demonstrate these effects *in vivo*, which is supported by the finding that Fhl2 has no effect on proliferation or differentiation of osteoblasts *in vivo*. Furthermore, the unspecific effect in cell culture observed by Lai may also indirectly influence mineralization and expression of osteocalcin.

Contrary to these teachings, the inventors of the present application have shown a direct specific cell-autonomous and anabolic effect of Fhl2 on the activity of already differentiated osteoblasts *in vitro* and *in vivo*. In addition, the present inventors are able to present a molecular mechanism for this observed effect. It is also noteworthy that the present inventors could not detect any Fhl2 effect on proliferation of differentiation of osteoblasts or osteoblast precursors *in vivo* which contradicts the *in vitro* data of Amaar.

For the above reasons, it is clear that the cited references fail to teach the claimed identification method. In fact, neither Amaar nor Lai teach or suggest a method of identifying a compound that promotes the capability of osteoblasts to form an

extracellular matrix via determining the Fhl2 protein levels. Since each and every aspect of the claimed invention is not specifically taught by the cited references, either inherently or explicitly, the references cannot anticipate the claims.

For at least the foregoing reasons, Applicant respectfully submits that the subject matters of the Claims are not anticipated by Amaar et al., are therefore not unpatentable under 35 U.S.C. § 102, and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 102.

Conclusion

For at least the foregoing reasons, Applicant respectfully submits that the present patent application is in condition for allowance. An early indication of the allowability of the present patent application is therefore respectfully solicited.

If Examiner Hiriyanna believes that a telephone conference with the undersigned would expedite passage of the present patent application to issue, he is invited to call on the number below.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is hereby authorized to charge fees necessitated by this paper, and to credit all refunds and overpayments, to our Deposit Account 50-2821.

Respectfully submitted,

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